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Young obese patients may benefit from GnRH-a long protocol contributing to higher implantation rate and live birth rate of fresh IVF-ET cycles☆

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ABSTRACT

Introduction: Obesity has detrimental influences on women reproductive health. There is little experience in optimizing controlled ovarian hyperstimulation (COH) protocols to treat Chinese obese patients who are undergoing in vitro fertilization and embryo transfer (IVF-ET) therapy.
Methods: The clinical outcome differences were retrospectively analyzed among obese patients who received gonadotrophin-releasing hormone agonist (GnRH-a), GnRH antagonist (GnRH-ant), micro dose GnRH-a (mGnRH-a) and GnRH-a long protocol in IVF-ET cycle at Chengdu Jinjiang Hospital for Women's and Children's Health from January 2014 to December 2019.
Results: The transplantation rate of the GnRH-a long protocol group (59.1%) was higher than that of the GnRH-ant (25.9%) and mGnRH-a (36.7%) groups. The total live birth rate of the GnRH-a long protocol group (46.2%) was higher than that of the GnRH-a group (25.9%) and GnRH-ant group (40.3%). The total number of frozen embryos in the GnRH-ant group was higher than in the other groups ($P < 0.05$). After adjusting for confounding factors, the logistic regression analysis showed that the GnRH-a long protocol group had higher probabilities of biochemical pregnancy, clinical pregnancy, and live birth than the GnRH-a protocol group. The Gn dose in the mGnRH-a group was higher than the other three groups. Whether single or twin, there were similar neonatal outcomes among the four groups including premature birth rate, Apgar score, newborn weight, and length.

☆ Ethical Review Board.

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Conclusion: For young obese patients undergoing IVF-ET, the GnRH-a long protocol for COH gives better pregnancy outcomes.

Abbreviations

COH	controlled ovarian hyperstimulation
IVF-ET	vitro fertilization and embryo transfer
mGnRH-a	micro dose gonadotrophin-releasing hormone agonist
GnRH-ant	gonadotropin-releasing hormone antagonist
HCG	human chorionic gonadotropin
AMH	anti-Müllerian hormone
AFC	antral follicle count
FSH	follicle-stimulating hormone
LH	luteinizing hormone
E2	estradiol
P	progesterone
ART	assisted reproductive treatment
LIF	leukemia inhibitory factor
Gn	gonadotropin

1. Introduction

The World Health Organization reported that approximately 13% of the global adult population (11% men and 15% women) were obese [1], and more than 50% of these women are overweight or obese at gestational age [2,3]. Obese women have impaired fertility or infertility due to anovulation, irregular menstruation, oocyte development disorders, and other factors [4–7]. A number of infertile obese people are seeking in vitro fertilization and embryo transfer (IVF-ET) for help. As one of the most important fundamental aspects of IVF-ET, an appropriate controlled ovarian hyperstimulation (COH) protocol optimization for obese patients [8,9] has remained controversial.

There are four commonly used ovulation protocols: GnRH agonist (GnRH-a) protocol, gonadotropin-releasing hormone antagonist (GnRH-ant) protocol, micro dose GnRH-a protocol (mGnRH-a), and GnRH-a long protocol. Each of these four protocols has its own characteristics. Although studies have reported that using GnRH-ant takes a shorter time than using GnRH-a and significantly reduced the incidence of ovarian hyperstimulation syndrome [10,11], pregnancy outcomes remain poorer in obese women compared to normal-weight women [12]. Several reports have also shown that patients with body mass index (BMI) > 25 kg/m^2 achieved similar clinical pregnancy rates with the choice of GnRH-ant or GnRH-a protocol [13,14]. However, two other retrospective cohort studies concluded that the GnRH-ant and GnRH-a protocols are recommended for obese patients undergoing IVF-ET [15,16]. Other studies comparing pregnancy outcomes of the general population after different doses and lengths of GnRH use have also shown inconsistent findings [17–19]. There are very few reports comparing the clinical efficacy and pregnancy outcomes of the four COH regimens in obese patients, and the conclusions on the optimal protocol in general patients were also inconsistent [20–22].

In addition, to the best of our knowledge, no study has compared the four protocols in the obese population. Therefore, this study aimed to retrospectively analyze the pregnancy outcomes of obese patients undergoing different COH protocols and aid clinicians in tailoring appropriate ovarian stimulation protocols to obese patients.

2. Materials and methods

2.1. Patients

This retrospective cohort study reviewed the data of patients who underwent IVF-ET between January 2014 and December 2019 at Chengdu Jinjiang Hospital for Women's and Children's Health in Sichuan, China, which includes four centers, named Gaoxin, Jingxiu, Sanguantang, and Xinan. The inclusion criteria were as follows: BMI≥ 30 kg/m^2 who underwent their first IVF-ET cycle and ages were 20–35 years as preventing study bias from age [23]. Exclusion criteria were as follows: patients who underwent intracytoplasmic sperm injection (ICSI) or rescue ICSI cycles; endometrial thickness <8 mm before transplantation [24]; COH, micro-stimulation protocol or natural cycle protocol; and genital malformation or uterine abnormality.

All data were obtained for clinical purposes, and all the procedures that have been performed were part of routine care. The study was approved by the Ethics Committee of the Chengdu Jinjiang Maternal and Child Health Hospital.

2.2. Stimulation protocols, oocyte retrieval, embryo transfer, luteal support

Clinical treatments are described as the previous study [25]. Briefly, for GnRH-a protocol group (A), 0.1 mg GnRH-a was injected intramuscularly in the luteal phase or on the 16th to 18th day of oral contraception. Fourteen days later, ultrasound and hormone level examinations were performed, and Gn was used to promote ovulation after attending the pituitary downregulation standard. For GnRH-ant protocol group (B), on the 2nd–3rd day of menstruation, Gn was used to stimulate follicle growth. When the follicle was larger than 12 mm or on the 6–7th day of using Gn, 0.25 mg antagonist was added until the trigger day. For GnRH-a long protocol group (C), 3.75 mg GnRH-a was injected on the 3rd–5th day of menstruation, and ultrasound and hormone level examinations were performed after 28 days. After meeting the pituitary downregulation standard, Gn was used to promote ovulation. For mGnRH-a protocol group (D): GnRH-a (0.625 mg) was injected intramuscularly in the luteal phase or on the 16th to 18th day of oral contraception. Ultrasound and hormone level examinations were performed on the 3rd day of menstruation, and Gn was used to promote ovulation.

Transvaginal ultrasound-guided oocyte retrieval and IVF fertilization were performed 34–36 h after the trigger. Seventy-two hours after oocyte retrieval, embryos were rated and 1–2 of them were selected for transfer. Luteum support was provided on the day of oocyte retrieval.

2.3. Follow-up

On the 14th day after embryo transfer, serum human chorionic gonadotropin (HCG) was measured to determine whether the patients were biochemically pregnant. Twenty-eight days after transplantation, vaginal ultrasound was used to determine whether the

Table 1
General data and clinical data of different groups.

	A (n = 148)	B (n = 239)	C (n = 66)	D (n = 30)	Test statistics	P value
BMI of woman (kg/m^2) *	31.23(30.47–32.19)	31.42 (30.44–33.28)	31.25 (30.48–32.89)	31.52(30.48–32.53)	2.916	0.405
Age (years) *	29(27–32)	28(26–31)	29(26.75–31.00)	31(27.75–33.25)a	12.175	0.007
Types of infertility* *					6.396	0.094
Primary	73(49.3)	136(56.9)	39(59.1)	11(36.7)		
Secondary	75(50.7)	103(43.1)	27(40.9)	19(63.3)		
Years of infertility (years) *	4(2–6)	4(2–5)	4(2–6)	4(2–7)	1.860	0.602
Diagnosis of infertility**					91.605	<0.001
PCOS	47(31.8)	115(48.1)	17(25.8)	1(3.3)		
Tubal	84 (56.8)	54(22.6)	23(34.8)	18(60.0)		
Male factor	5(3.4)	2(0.8)	5(7.6)	0(0.0)		
Mixed/Unexplained/Other	12(8.1)	68(28.5)	21(31.8)	11(36.7)		
OHSS**	6 (4.1)	6 (2.5)	0 (0.0)	0 (0.0)	2.798	0.351
Number of oocytes obtained (pieces)*	11 (6–15) b	11 (6–18) b	9 (6–14)	7 (3.75–9.25)	16.829	0.001
Number of embryos transferred* * *					59.292	<0.001
0.00	63(42.6)ab	177(74.1)	27(40.9)ab	19(63.3)		
1.00	6(4.1)	13(5.4)	1(1.5)	2(6.7)		
2.00	79(53.4)ab	49(20.5)	38(57.6)ab	9(30)		
Total frozen embryos* * *	2.5(1v6)	4(1–7)	1(0–3.25)ac	1(0–2.25)a	26.879	<0.001
No. of Day3 frozen embryos ***	1(0–2)	1(0–2)	0(0–0.25)ac	0 (0–2)	19.614	<0.001
No. of Day5/6 frozen embryos ***	2(0–4)b	2(0–6)b	1(0–2.25)a	0(0–1)	22.127	<0.001
GN dose*	2187.5(1725–2756.25) b	2325(1800–3000) b	2350(1800–3075) b	3225 (2606.25–3900)	22.964	<0.001
GN days*	10 (9–11.75)	10 (9–11)	12 (10–13)ac	12 (9.75–14)ac	38.987	<0.001
AMH (ng/mL) *	4.37(2.95–5.49)b	5.25(2.78–8.17)b	3.55(2.51–5.32)ab	1.65(1.06–2.25)	49.370	<0.001
AFC (PCs) *	18.5(13–26.75)ab	24(14–34)b	19(13–26)b	8(7–11)	62.399	<0.001
FSH (miU/ml) *	5.82(4.98–6.82)	6.61(5.45–7.51)c	6.32(4.82–7.49)	7.165(5.85–9.21)c	20.054	<0.001
LH (miU/ml) *	4.04(2.56–5.86)	4.12(2.68–7.8)	2.955(2.21–5.06)a	3.3(2.0–4.55)	13.489	0.004
E2 (pg/ml) *	46(34–58.62)	45(36–59)	43.5(29.00–54.25)	37(20–53)	7.865	0.049
P (ng/ml) *	0.64(0.41–0.91)	0.59(0.35–0.84)	0.61(0.33–0.88)	0.54(0.31–0.76)	5.205	0.157

Note: non-normal distributions are described statistically by median (IQR), classified variables are presented with the number of case (%); *Kruskal–Wallis rank sum test; **Pearson chi-square test; ***Fisher exact probability method; A: GnRH-a protocol group, B: GnRH-ant protocol group, C: GnRH-a long protocol group, D: mGnRH-a protocol group (Micro dose GnRH-a protocol; a: $P < 0.05$ vs. B group; b: $p < 0.05$ vs. D group; c: $p < 0.05$ vs. A group).

patient was pregnant. A dedicated nurse would follow up with the patient by telephone twice, 4 months after confirmation of clinical pregnancy and after the birth of the baby according to the expected date of confinement. The call-back nurse records the patient's pregnancy and neonatal outcomes, including live birth, miscarriage, ectopic pregnancy, early abortion (<12 weeks), late abortion (12 and 28 weeks), and fetal length, weight, and Apgar scores.

2.4. Outcome parameters

The primary outcome measure was the total live birth rate, defined as the birth of at least one live baby after 24 weeks of gestation.

The secondary outcome measures included the total live birth rate, biochemical pregnancy, clinical pregnancy, and ectopic pregnancy. Biochemical pregnancy was defined as positive serum β-HCG level (β-HCG ≥5 U/L) at 14 days after transplantation. Clinical pregnancy was defined as the presence of at least one gestational sac in the uterine cavity confirmed by vaginal ultrasound at 28 days of gestation, with an embryonic bud and primordial heartbeat. Ectopic pregnancy was defined as a gestational sac observed on ultrasonography outside the uterus. Miscarriage was defined as clinical pregnancy loss by the 24th week of gestation.

2.5. Statistical analysis

Normal distribution data are presented as mean ± SD, and a one-way analysis of variance was used for comparison between groups. Continuous variables with non-normal distribution are described statistically by median (IQR), and nonparametric tests (Kruskal–Wallis rank sum test) were used for comparison between groups. For classified variables, the number of cases (percentage) was used, and the Pearson chi-square test or Fisher exact probability test was used for comparison between groups. When there was a statistical difference in the overall rate between groups, further multiple comparisons were made using the partitions of χ^2 method, and the P value of the comparison was corrected by the Bonferroni method. Multivariate logistic regression was used to analyze the relationship between the four COH programs and pregnancy outcomes, and confounding factors were adjusted. All statistical analyses were performed using the statistical package social sciences (SPSS) version 25.0. Statistical significance was set at $P < 0.05$ (two-tails).

3. Results

3.1. General and clinical characteristics of patients in different groups

A total of 483 cycles (obese patients) were analyzed, including 148 in the GnRH-a protocol group (A), 239 in the GnRH-ant protocol group (B), 66 in the GnRH-a long protocol group (C), and 30 in the mGnRH-a protocol group (D). As shown in Table 1, the diagnoses of infertility were statistically different in the four groups. The proportion of PCOS was 31.8% in the A group, 48.1% in the B group, 25.8% in the C group, and 3.3% in the D group. Although six cases of ovarian hyperstimulation syndrome (OHSS) occurred in both groups A and B, there was no statistical difference in the incidence of OHSS among the four groups ($P = 0.351$). The total number of frozen embryos in group B was larger than that in groups D and C ($P < 0.05$). The total number and the number of day 3 frozen embryos of group C was less than those of groups A and B ($P < 0.05$), and the number of Day 5/Day 6 frozen embryos was lower than that of group B ($P < 0.05$). Besides, the results showed statistically significant differences in the number of oocytes obtained (pieces), the number of embryos transferred, GN dose, GN days, AMH (ng/mL), AFC (PCs), FSH (miU/ml), LH (miU/ml), and E_2 (pg/ml). However, there was no statistical significance between the four groups in terms of BMI of the woman (kg/m2), types of infertility, years of infertility, and P (ng/ml).

3.2. Comparison of pregnancy rate between different groups

As shown in Table 2, the embryo-free availability rate of group A was significantly lower than that of the other three groups (p <

Table 2
Comparison of pregnancy outcomes among four groups.

	A(n = 148)	B(n = 239)	C(n = 66)	D(n = 30)	Test statistics	P value
Embryo-free availability * * *	0/148(0.0)a	11/239(4.6)b	3/66(4.5)b	1/30(3.3)b	9.000	0.018
Transplant rate * *	85/148(57.4)a	62/239(25.9)b	39/66(59.1)a	11/30(36.7)b	48.156	<0.001
Total live birth rate* * *	22/85(25.9)a	25/62(40.3)a	18/39(46.2)b	3/11(27.3)ab	12.577	0.004
Live birth rate of single * * *	18/85(21.2)ab	16/62(25.8)b	14/39(35.9)a	2/11(18.2)ab	12.339	0.004
Live birth rate of twin* * *	4/85(4.7)	9/62(14.5)	4/39(10.3)	1/11(9.1)	3.030	0.336
Biochemical pregnancy rate * *	41/85(48.2)	33/62(53.2)	25/39(64.1)	5/11(45.5)	2.952	0.399
Clinical pregnancy rate * * *	30/85(35.3)	29/62(46.8)	23/39(59.0)	3/11(27.3)	7.434	0.055
Ectopic pregnancy rate * * *	3/41(7.3)	2/33(6.1)	0/25(0.0)	0/5(0.0)	1.932	0.633
Total abortion rate * * *	4/30(13.3)	2/29(6.9)	5/23 (21.7)	0/3 (0.0)	5.679	0.560
Early abortion rate * * *	4/30(13.3)	2/29(6.9)	4/23(17.4)	0/3(0.0)	1.639	0.676
Late abortion rate * * *	0/30(0.0)	0/29(0.)	1/23(4.3)	0/3(0.0)	3.904	0.306

Note: Data are number (%); **Pearson chi-square test; ***Fisher exact probability method; there was no statistically significant difference between groups with the same corner letters, and a significant difference between groups with different corner letters; A: GnRH-a protocol group; B: GnRH-ant protocol group; C: GnRH-a long protocol group; D: mGnRH-a protocol group (Micro dose GnRH-a protocol).

0.05). The transplantation rate of group C (59.1%) was higher than that of group B (25.9%) and group D (36.7%), and the difference was statistically significant ($p < 0.05$). The transplantation rate (57.4%) in group A was also higher than that in groups B and D ($p < 0.05$). The total live birth rate in group C (46.2%) was significantly higher than that of groups A (25.9%) and B (40.3%) ($P < 0.05$), and was also higher than that of group D (27.3%), with no statistical significance. The single birth rate of group C (35.9%) was significantly higher than that of group B (25.8%) ($p < 0.05$). There was no significant difference in the birth rate of twins among the groups. There were no significant differences among the four groups in other pregnancy outcomes, including biochemical pregnancy rate, clinical pregnancy rate, ectopic pregnancy rate, total abortion rate, early abortion rate, and late abortion rate.

3.3. Multivariate analysis of pregnancy outcome

The results of the multifactor logistic regression analysis are presented in Table 3. The probability of biochemical pregnancy in group C was 2.619 times higher than that in group A, [aOR 95%CI 2.619 (1.010–6.794), $p = 0.048$], and the probability of clinical pregnancy was 3.437 times higher than that in group A [aOR 95%CI 3.437 (1.329–8.891), $p = 0.011$], and the probability of live birth was 2.914 times higher than that of group A [aOR 95%CI 2.914 (1.114–7.624), $p = 0.029$]. In general, after adjusting for confounding factors, group C (GnRH-a long protocol group) had better pregnancy outcomes than group A (GnRH-a protocol group).

4. Neonatal outcomes in different groups

Regardless of single birth or twin, the four protocols had similar neonatal outcomes, and there were no statistical differences in premature birth rate, length (cm), newborn weight (kg), and Apgar score (points).

5. Discussion

The BMI and obesity rates in China have been rising steadily Since the 1980s [26,27]. Between 2004 and 2018, standardized mean BMI levels increased from 22.7 kg/m^2 (95 CI 22·5–22·9) to 24.4 kg/m^2 (24.3–24.6), and the prevalence of obesity from 3.1% (2.5%–3.7%) to 8.1% (7.6%–8.7%) [28]. It has been controversial which COH protocol is optimal for infertile obese patients undergoing assisted reproductive treatment (ART) therapy.

The present study showed that the GnRH-a long protocol group (C) had significantly better pregnancy outcomes, including a higher transplant rate and much higher probabilities of biochemical pregnancy, clinical pregnancy, and live birth. Consistently, a previous study comparing the GnRH-a long protocol with the GnRH-ant protocol in patients with BMI >25 kg/m^2 showed that the GnRH-a long protocol group had a higher transplant rate (25.7% vs. 15.6%; $P < 0.01$) and clinical pregnancy rate (41.3% vs. 28.8%; $p < 0.01$) [16]. A recent retrospective cohort study also found that only BMI was significantly associated with a live birth in patients with low ovarian response under the age of 35, and the GnRH-a long protocol group achieved a significantly higher cumulative live birth rate than the GnRH-ant protocol group [29]. Actually, studies comparing the outcomes of different COH protocols in obese patients are relatively limited, and previous studies in normal-weight patients have similarly found that the GnRH-a long protocol had better pregnancy outcomes than the GnRH-a protocol and mGnRH-a protocol [30]. Another study compared the effects of the GnRH-a long protocol, the GnRH-ant protocol, and the mGnRH-a protocol in poor responders and again showed that the GnRH-a long protocol had statistically higher clinical pregnancy and live birth rates [31]. The rationale of GnRH-a long protocol is to use a longer duration of GnRH-a to regulate the pituitary gland and stimulate follicle growth with exogenous gonadotropins, avoiding the surge of endogenous luteinizing hormone (LH) before oocyte retrieval [32]. Previous evidence suggests that a short duration or small dose of GnRH-a results in incomplete down-regulation and early LH peaks, leading to an increased cycle cancellation rate [33]. Appropriate prolongation of GnRH-a administration can increase the synchronism of follicle development [34], improve the quality of oocytes and embryos [35], and increase the live birth rate [17,36]. Another study supports that increased GnRH-a concentrations can restore endometrial physiological secretion and improve uterine receptivity [37]. In our study, the GnRH-a long protocol used a higher dose and longer duration of GnRH-a compared to other protocols, which may have contributed to its better pregnancy outcome. Another reason for obtaining better pregnancy results may be the lower luteinizing hormone (LH) levels in the GnRH-a long protocol group. It is known that relatively high LH serum levels have a significant impact on pregnancy success [38]. The mechanism is that the expression level of the LH receptor is closely related to oocyte morphology, oocyte maturity, and fertilization rate, and is affected by different ovarian

Table 3
Multivariate Logistic regression analysis of pregnancy outcome.

Group	Biochemical pregnancy		Clinical pregnancy		Live birth	
	aOR (95%CI)	P	aOR (95%CI)	P	aOR (95%CI)	P
A	Reference		Reference		Reference	
B	1.16 (0.535–2.517)	0.707	1.516 (0.69–3.33)	0.300	2.057 (0.907–4.664)	0.084
C	2.619 (1.010–6.794)	0.048	3.437 (1.329–8.891)	0.011	2.914 (1.114–7.624)	0.029
D	0.831 (0.203–3.408)	0.797	0.594 (0.125–2.808)	0.511	1.102 (0.232–5.245)	0.903

Note: adjusted odds ratio; CI, confidence interval; adjusting variables in the model were: age, diagnosis of infertility, number of transplanted embryos (1 = 0, 2 = 1), GN quantity, days of GN, AMH (ng/mL), AFC (PCs), FSH (miU/L), LH (miU/mL); A: GnRH-a protocol group; B: GnRH-ant protocol group; C: GnRH-a long protocol group; D: mGnRH-a protocol group (Micro dose GnRH-a protocol).

stimulation protocols [39]. Previous publications have shown that a higher pregnancy success rate can be achieved if the premature surge of endogenous LH can be suppressed [40,41]. These mechanisms may explain why we observed better pregnancy outcomes in the GnRH-a long protocol.

In addition, we found that all four protocols used in this study had a higher Gn dose than normal weight patients reported in other studies, consistent with previous studies [42–44]. This may be related to the volume of the distribution or peripheral metabolic clearance [45]. Obese patients have a large weight base and need to be given higher drug doses to obtain adequate blood concentrations. It has been reported that increasing GnRH-a usage leads to longer ovulation promotion times and increased Gn dose requirements [46], and our data indeed show that the GnRH-a long protocol group has longer GN days and higher GN amounts. This adequate stimulation of the ovary to induce follicle development and oocyte maturation, producing higher quality and quantity of oocytes, maybe another reason for the better outcome in the GnRH-a long protocol group.

Moreover, our study compared the neonatal outcomes of the four protocols and the results showed no differences between them (Table 4), and no malformed fetuses or maternal deaths occurred (not listed in the table). Given that the GnRH-a long protocol group has better pregnancy outcomes (including higher implantation and live birth rates) and is more cost-effective [47], we recommend it as the COH protocol for young obese patients. Although the GnRH-a long protocol has better pregnancy outcomes, studies have shown that in GnRH-a long protocol patients, overweight and obesity are associated with unfavorable IVF outcomes (including lower implantation rates, clinical pregnancy rates, and live birth rates) compared to normal-weight patients [48,49]. Therefore, we recommend that obese patients lose as much weight as possible before proceeding to assisted reproductive conception.

6. Conclusions

By comparing not only pregnancy outcomes but also neonatal outcomes among four protocols, we found that GnRH-a long protocol group has better pregnancy outcomes (including higher implantation rate and live birth rate) in Chinese infertile women. It suggested that GnRH-a long protocol group is priorly recommended for young obese infertile women in fresh IVF-ET cycles. However, because of the retrospective nature of this cohort study, the choice of a patient's COH protocol was determined by the doctor based on their AMH level and factors such as age and not a random assignment. Therefore, this conclusion requires more randomized controlled trials (RCTs) and prospective studies in the future to validate.

Informed consent

This research study was conducted retrospectively from data obtained for clinical purposes. All the procedures that have been performed were part of the routine care and obtained the patient's consent before starting treatment.

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Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013).

The study was approved by the Ethics Committee of the Chengdu Jinjiang Maternal and Child Health Hospital and informed consent was taken from all the patients.

Table 4
Comparison of neonatal outcomes among four groups.

	A	B	C	D	Test statistics	P value
Single						
Premature birth rate (.)	1/18 (5.55)	5/16 (31.25)	1/14 (7.14)	0/2 (0.00)	4.770	0.172
Body length (cm)	49.72 ± 1.90	49.63 ± 2.39	49.79 ± 2.52	50.00 ± 0.00	0.024	0.995
Weight of newborn (kg)	3.33 ± 0.65	3.48 ± 0.66	3.31 ± 0.55	3.43 ± 0.11	0.235	0.871
Apgar score (points)	9.56 ± 0.62	9.69 ± 0.70	9.86 ± 0.36	10.00 ± 0.00	0.889	0.454
Twin						
Premature birth rate (%)	3/4 (75.00)	7/9 (77.78)	1/4 (25.00)	0/1 (0.00)	4.741	0.187
Body length (cm)	48.13 ± 2.58	45.56 ± 3.56	48.5 ± 2.38	48.50	1.358	0.296
Weight of newborn (kg)	0.85 ± 0.12	2.56 ± 0.25	2.7 ± 0.25	3.25	2.837	0.076
Apgar score (points)	48.13 ± 2.58	9.78 ± 0.67	9.13 ± 1.03	10.00	2.471	0.105

Note: Data are number (%) or mean ± SD; **Pearson chi-square test; ***Fisher exact probability method; there was no statistically significant difference between groups with the same corner letters, and a significant difference between groups with different corner letters; A: GnRH-a protocol group; B: GnRH-ant protocol group; C: GnRH-a long protocol group; D: mGnRH-a protocol group (Micro dose GnRH-a protocol).

Author contribution statement

Conceived and designed the experiments: Qi Wan, Yue Qian, Li Tan, Ming-Jing Xia, Xiang-Qian Meng, Yu-Bin Ding, Zhao-Hui Zhong, Lihong Geng; Performed the experiments: Qi Wan, Yue Qian, Li Tan, Ming-Jing Xia, Xiang-Qian Meng, Yu-Bin Ding, Zhao-Hui Zhong, Lihong Geng; Analyzed and interpreted the data: Qi Wan, Yue Qian, Li Tan, Ming-Jing Xia, Xiang-Qian Meng, Yu-Bin Ding, Zhao-Hui Zhong, Lihong Geng; Contributed reagents, materials, analysis tools or data: Qi Wan, Yue Qian, Li Tan, Ming-Jing Xia, Xiang-Qian Meng, Yu-Bin Ding, Zhao-Hui Zhong, Lihong Geng; Wrote the paper: Qi Wan, Yue Qian, Li Tan, Ming-Jing Xia, Xiang-Qian Meng, Yu-Bin Ding, Zhao-Hui Zhong, Lihong Geng.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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